NIDN-10389

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	O. Axelsson, et al.	Group Art Unit:	To be assigned
Serial Number:	To be assigned	Examiner:	To be assigned
Filing Date:	November 16, 2001		
Title:	Methods of Magnetic Resonance Imaging (MRI) Using Contrast Agent Solutions Formed from the Dissolution of Hyperpolarized Materials		

FIRST PRELIMINARY AMENDMENT

Honorable Assistant Commissioner of Patents
Box Patent Application
Washington, D.C. 20231

Sir:

Please consider the following amendments and remarks in connection with the prosecution of the captioned application, which is a continuation of international application number PCT/GB00/01888 filed May 17, 2000. This application also claims priority to application number 9911682.4 filed May 19, 1999 in Great Britain and application number 9916567.2 filed July 14, 1999 in Great Britain. Additionally, this application claims the benefit of United States provisional application numbers 60/139,258 filed June 15, 1999 and 60/146,947 filed August 2, 1999.

In the Specification

Please amend page 1, line 5, by inserting the following sentence and heading:

-- This application is a continuation application of international application number PCT/GB00/01888 filed May 17, 2000, the entire disclosure of which is hereby incorporated by reference.

Background of Invention--

Please amend page 2, lines 1-6, as follows:

polarising agents, for example OMRI contrast agents (see, e.g. WO 98/58272 to the present Applicant) or hyperpolarised gases to achieve *ex vivo* nuclear spin polarisation of non zero nuclear spin nuclei in an administrable MR imaging agent. By polarising agent is meant any agent suitable for performing *ex vivo* polarisation of an MR imaging agent.

Please amend page 4, line 13, by inserting the following heading:

--Summary of Invention--

Please amend page 7, line 15, by inserting the following paragraph and headings:

--Brief Description of the Figures

Figure 1 is a schematic diagram showing the interactions between the electronic singlet and triplet states of a photoactive molecule;

Figure 2 presents plots of absorption and nuclear polarization showing the solid effect in its pure form;

Figure 3 presents plots of absorption and nuclear polarization showing the differential solid effect;

Figure 4 shows the energy levels of Ni^{2+} in sapphire when the c-axis is parallel to the field direction; and

Figure 5 shows the energy levels of Ni^{2+} in sapphire when the c-axis is perpendicular to the field direction.

Detailed Description of the Invention--

Please amend page 35, line 13, by deleting the following text:

[Figure 1 is a schematic diagram showing the interactions between the electronic singlet and triplet states of a photoactive molecule;

Figure 2 shows the solid effect in its pure form;

Figure 3 shows the differential solid effect;

Figure 4 shows the energy levels of Ni^{2+} in sapphire when the c-axis is parallel to the field direction; and

Figure 5 shows the energy levels of Ni^{2+} in sapphire when the c-axis is perpendicular to the field direction.]

Please amend page 35, line 22, by inserting the following heading and paragraph:

--Examples

The following examples illustrate certain preferred embodiments of the instant invention but are not intended to be illustrative of all embodiments.--

Please amend page 37, line 25, by inserting the following paragraph:

-- It is apparent that many modifications and variations of the invention as hereinabove set forth may be made without departing from the spirit and scope thereof. The specific embodiments described are given by way of example only, and the invention is limited only by the terms of the appended claims.--

In the Claims

Please amend page 38, line 1, as follows:

[Claims]

What is claimed is:

Please cancel claims 1-34, without prejudice.

Please add new claim 35 as follows:

35. (new) A method of magnetic resonance investigation of a sample, preferably of a human or non-human animal body, said method comprising:

(i) nuclear spin polarising a solid MR imaging agent;

(ii) administering the nuclear spin polarised MR imaging agent to said sample;

(iii) exposing said sample to a radiation at a frequency selected to excite nuclear spin transitions in the spin polarised nuclei of the MR imaging agent;

(iv) detecting magnetic resonance signals from said sample; and

(v) generating an image, dynamic flow data, diffusion data, perfusion data, physiological data or metabolic data from said detected signals,

wherein said polarising step (i) is carried out by

(a) spin refrigeration, or by,

(b) irradiating with circularly polarised light.

Please add new claim 36 as follows:

36. (new) The method of claim 35 wherein said agent is administered to said sample after dissolution in water.

Please add new claim 37 as follows:

37. (new) The method of claim 35 wherein said agent further comprises other pharmaceutical additives.

Please add new claim 38 as follows:

38. (new) The method of claim 35 wherein said solid MR imaging agent is a water-soluble high T_1 agent.

Please add new claim 39 as follows:

39. (new) The method of claim 35 wherein said MR imaging agent retains its polarisation when transported in a substantially uniform magnetic field and at a low temperature.

Please add new claim 40 as follows:

40. (new) The method of claim 39 wherein said magnetic field is greater than 10 mT.

Please add new claim 41 as follows:

41. (new) The method of claim 39 wherein said magnetic field is greater than 1T.

Please add new claim 42 as follows:

42. (new) The method of claim 39 wherein said temperature is lower than 80°K.

Please add new claim 43 as follows:

43. (new) The method of claim 39 wherein said temperature is lower than 4.2°K.

Please add new claim 44 as follows:

44. (new) The method of claim 36 wherein a magnetic field is present during the dissolution stage.

Please add new claim 45 as follows:

45. (new) The method of claim 35 wherein step (i) comprises:

(i) irradiating a solid compound having a singlet electronic ground state and containing a non zero nuclear spin nucleus with light to generate an excited polarized triplet electronic state of said agent;

(ii) transforming electronic polarization of said solid compound into a nuclear spin polarization in a soluble MR imaging agent to form a nuclear spin polarised MR imaging agent;

(iii) dissolving said polarised MR imaging agent in an aqueous medium.

Please add new claim 46 as follows:

46. (new) The method of claim 35 wherein said step (ii) is carried out after the MR imaging agent is dissolved in a physiologically tolerable solvent.

Please add new claim 47 as follows:

47. (new) The method of claim 35 wherein said step (ii) is carried out after the MR imaging agent is separated from some or all of the paramagnetic species or chromophores.

Please add new claim 48 as follows:

48. (new) The method of claim 46 wherein the solution formed retains its polarisation in frozen form.

Please add new claim 49 as follows:

49. (new) An apparatus for use in the method of claim 35 when the polarising of a MR agent is by spin refrigeration, the apparatus comprising:

(i) a chamber cooled to a temperature preferably lower than 80K disposed in the primary magnetic field of MR apparatus, or in a separate magnetic field, of strength 0.2T or more;

and wherein said chamber is:

(i) adapted to receive particulate solid MR imaging agent, doped with or intimately mixed with paramagnetic polarising agent;

(ii) rotates said agent about an axis non-parallel with the primary field or passes said agent through a conduit such that it rotates in that way or

mixes said agent such that it rotates in that way, or, where the chamber is in a separate magnetic field, rotates the magnetic field about one or more axes;

(iii) dissolves said polarised solid agent in or passes it to a mixing chamber, where it is dissolved in a physiologically tolerable solvent;

(iv) passes the solution thus formed through or over an immobilised paramagnetic metal binding agent and/or through a filter;

(v) and into the conduit for administration into a sample situated within the primary magnetic field of the MR imager.

Please add new claim 50 as follows:

50. (new) The apparatus of claim 49 wherein said chamber is cooled to lower than or equal to 1°K.

Please add new claim 51 as follows:

51. (new) The apparatus of claim 49 wherein the strength of said magnetic field is 0.5 to 10T.

Please add new claim 52 as follows:

52. (new) A process for the preparation of a nuclear spin polarised MR imaging agent, said process comprising:

irradiating a solid compound having a singlet electronic ground state and containing a non zero nuclear spin nucleus with light to generate an excited polarized triplet electronic state of said agent;

transforming electronic polarization of said solid compound into a nuclear spin polarization in a soluble solid MR imaging agent to form a nuclear spin polarised MR imaging agent, optionally dissolving said MR imaging agent in an aqueous medium (preferably a physiologically tolerable medium), and optionally storing said polarised MR imaging agent at a reduced temperature and at a magnetic field of greater than 10 mT.

Please add new claim 53 as follows:

53. (new) The process of claim 52 wherein said reduced temperature is liquid nitrogen temperature or below.

Please add new claim 54 as follows:

54. (new) The process of claim 52 wherein said reduced temperature is liquid helium temperature.

Please add new claim 55 as follows:

55. (new) The process of claim 52 wherein said magnetic field is greater than 2T.

Please add new claim 56 as follows:

56. (new) A process for the preparation of a polarised electronic triplet state of a solid compound having a singlet electronic ground state said process comprising irradiating said compound in a solid state with a first radiation of a wavelength selected to excite said compound from a ground singlet electronic state to an excited singlet electronic state and with a positively or negatively, circularly polarised second radiation of a wavelength selected to excite said compound from the lowest triplet electronic state to the next-to-lowest triplet electronic state.

Please add new claim 57 as follows:

57. (new) The process of claim 56 wherein said compound is a water-soluble compound containing at least one non-zero nuclear spin nucleus.

Please add new claim 58 as follows:

58. (new) A water-soluble MR imaging agent compound:

(i) containing a nuclear spin polarised I=½ nucleus;

(ii) having a molecular weight below 1000D;

(iii) containing a cyclic chromophore; and

(iv) having an nmr spectrum for said I=½ nucleus having a linewidth of less than 100 Hz.

Please add new claim 59 as follows:

59. (new) The agent compound of claim 58 wherein said molecular weight is below 500D.

Please add new claim 60 as follows:

60. (new) The agent of claim 58 wherein said cyclic chromophore is heterocyclic.

Please add new claim 61 as follows:

61. (new) The agent of claim 58 wherein said linewidth is below 1 Hz.

Please add new claim 62 as follows:

62. (new) A physiologically tolerable MR imaging composition comprising the nuclear spin polarised MR imaging agent of claim 58 dissolved in water together

with one or more physiologically tolerable excipients, said imaging agent containing nuclei of a I=½ isotope characterised in that said nuclei are polarised such that their nmr signal intensity is equivalent to a signal intensity achievable in a magnetic field of at least 0.1T.

Please add new claim 63 as follows:

63. (new) The composition of claim 62 wherein said nuclei are at higher than natural abundance.

Please add new claim 64 as follows:

64. (new) The composition of claim 62 wherein said magnetic field is at least 450T.

Please add new claim 65 as follows:

65. (new) The composition of claim 62 wherein said composition is sterile and is stable at a physiological temperature.

Please add new claim 66 as follows:

66. (new) A method of manufacture of an MR imaging composition for use in a method of diagnosis involving generation of a MR image by MR imaging of a

human or non-human animal body, wherein said method involves nuclear spin polarisation of an MR imaging agent by means of spin refrigeration.

Remarks

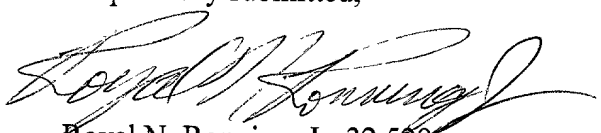
Applicants have amended the specification to cross reference the parent application which is a PCT application designating the United States. Applicants have also amended the specification to add the required headings and move the text to be in the required order.

Applicants have cancelled claims 1-34, without prejudice and have added new claims 35-66. A clean version of the claims is attached hereto.

Applicants are submitting herewith a copy of the International Search Report which issued on International Application number PCT/GB00/01888, of which the present application is a continuation. All of the publications cited in the International Search Report are listed on the attached Information Disclosure Statement.

Applicants respectfully assert that all amendments are fairly based on the specification, and respectfully request their entry.

Respectfully submitted,



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